



Protocol name: Pazopanib in High-Risk Prostate Cancer Followed by Radical Prostatectomy and Pelvic Lymph Node Dissection
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A Neoadjuvant, Randomized, Phase II Study of VEGF Tyrosine Kinase Inhibitor (Pazopanib) in Men with High-Risk Prostate Cancer Followed by Radical Prostatectomy and Pelvic Lymph Node Dissection

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LIST OF ABBREVIATIONS

Abbreviation or Term ¹	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca ⁺⁺	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl ⁻	Chloride
CL _{cr}	Creatinine clearance
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
EKG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO ₃ ⁻	Bicarbonate
HCV	Hepatitis C virus

Abbreviation or Term¹	Definition/Explanation
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IB	Investigator's Brochure
i.e.	Id est (that is)
INR	International normalized ratio
IRB	Institutional review board
MedRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
PD	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cell
QD	Once daily
QTc	QT interval corrected
SAE	Serious adverse event
SD	Standard deviation or stable disease
T ₄	Thyroxine
TID	Three times daily
TSH	Thyroid-stimulating hormone
WBC	White blood cell

All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

STUDY SUMMARY

Title	A Neoadjuvant Phase II Study of Pazopanib in Men With High-Risk Prostate Cancer Followed by Radical Prostatectomy and Pelvic Lymph Node Dissection
Short Title	Pazopanib in High-Risk Prostate Cancer Followed by Radical Prostatectomy and Pelvic Lymph Node Dissection
Protocol Number	IRB # 63129
IND	118456
Phase	Phase II
Design	Phase II, prospective, randomized, double blind, placebo controlled, two arm study.
Study Duration	Estimated duration for the main protocol is 16 months (14 month enrollment period, study duration is 2 months)
Study Center(s)	Single-center
Objectives	1) To determine if pazopanib can decrease the extent of pre-metastatic niche formation in benign lymph nodes in patients with high-risk, localized prostate cancer. Hypothesis: Treatment with pazopanib (as compared to control) will result in a decrease in pre-metastatic niche formation, as characterized by VEGFR1+ cell clusters, in pelvic lymph nodes
Number of Subjects	30 (15 patients per arm)
Diagnosis and Main Eligibility Criteria	<ol style="list-style-type: none"> 1. Men ≥ 18 years of age 2. Histological documentation of adenocarcinoma of the prostate, with available biopsy pathology. Biopsy material must be available for pathologic review. 3. All patients must meet one or more of the following disease features: clinical stage $\geq T3$; Primary Gleason score of 4 OR Gleason score of 8, 9 or 10; serum PSA ≥ 20 ng/mL; Prostate MRI findings consistent with T3 disease; Any clinical stage and PSA >10 and Gleason score 7; A Kattan nomogram predicted probability of being free from biochemical progression at 5 years after surgery of $< 60\%$.

	<ol style="list-style-type: none"> 4. Patients must have a PSA ≥ 2 ng/mL at the time of diagnosis of prostate cancer or later. 5. No prior radiation or chemotherapy for prostate cancer treatment. 6. Potential candidate for radical prostatectomy. 7. ECOG Performance Status of 0 or 1. 8. Patients may have been treated with up to 4 months of androgen deprivation therapy. 9. No clinical evidence of metastatic prostate cancer, or enlarged pelvic lymph nodes in the imaging studies. 10. Fresh resected lymph nodes must be provided for all subjects for biomarker analysis immediately (same day) after surgery (radical prostatectomy).
Study Product, Dose, Route, Regimen and duration	<u>Treatment Arm:</u> Pazopanib, 800 mg, orally daily for 28 days prior to radical prostatectomy.
Reference therapy	<u>Placebo Arm:</u> Placebo tablet orally, daily for 28 days prior to radical prostatectomy.
Statistical Methodology	<p>With 15 subjects per arm (30 subjects in all) there will be 80% power to detect a difference of 1.33 in the mean number of VEGFR+1 clusters/hpf between the reference and experimental arms using a student's t-test at the one-sided alpha = 0.05 significance level.</p> <p>Progression-free survival will be a secondary efficacy endpoint. PFS will be analyzed descriptively using Kaplan-Meier methods and associated 95% confidence intervals. Exploratory biomarker endpoints will be compared between the arms using student's t-tests (provided the data is normally distributed) or a non-parametric Wilcoxon test (if the data is non-normally distributed). Safety outcomes will be tabulated.</p> <p>An interim analysis will be done after 16 patients have enrolled to assess post-surgical toxicities.</p>

1 OBJECTIVES

1.1 Primary Objectives and Endpoints

- 1.1.1 To evaluate if pazopanib can decrease the extent of pre-metastatic niche formation in benign lymph nodes in patients with high-risk, localized prostate cancer. Hypothesis: Treatment with pazopanib (as compared to control) will result in a decrease in pre-metastatic niche formation, as characterized by VEGFR1+ cell clusters, in pelvic lymph nodes.

1.2 Secondary Objectives and Endpoint

- 1.2.1 Progression free survival, in terms of PSA recurrence
- 1.2.2 Safety and tolerability (adverse events during pazopanib treatment, and during intraoperative and post-operative period).

1.3 Exploratory Objectives and Endpoint

- 1.3.1 To evaluate if pazopanib therapy decreases the number of bone marrow derived cells (BMDCs), which initiate pre-metastatic niches in the benign pelvic lymph nodes. Hypothesis: Treatment with pazopanib will reduce the number of BMDCs in pelvic lymph nodes.
- 1.3.2 To evaluate if pazopanib therapy decreases levels of MDSCs and Tregs, immune cells that potentially suppress the antitumor immune response and thereby contribute to pre-metastatic niche formation, in benign lymph nodes. Hypothesis: VEGF-TKIs stifle recruitment of myeloid derived suppressor cells (MDSCs) to tumor tissue in murine xenografts models, and we thus suspect that pazopanib therapy will reduce MDSC recruitment.
- 1.3.3 To evaluate if pazopanib therapy results in improved clinical outcome. Hypothesis: Through impeding pre-metastatic niche formation, we suspect that pazopanib therapy will yield improvement in clinical endpoint such as progression free survival

2 BACKGROUND

2.1 Defining prognosis in prostate cancer.

Prostate cancer represents the most common malignancy in males. More than 241,000 men were diagnosed with prostate cancer in 2012 cancer, and 28, 170 were estimated to die of their disease, mainly because of progression to metastatic disease.[1] The incidence of prostate cancer rose sharply between 1990 and 1995, likely attributable to

an increase in widespread adoption of PSA screening. PSA screening has also resulted in a drastic stage migration in prostate cancer, with far fewer patients presenting with *de novo* metastatic disease.[2] While these data are encouraging, the increasing proportion of patients with localized disease underscores the need to develop accurate predictive tools to determine the risk of metastatic progression. Clinical guidelines, such as those published by the NCCN, employ risk stratification tools combining stage, grade and PSA to determine the risk of biochemical recurrence after definitive local therapy.[3] These tools have been validated in several series and provide a superior basis for treatment recommendations compared to clinical stage alone.[4,5] However, no currently available risk stratification schema has perfect accuracy, and furthermore, only a limited number can predict outcomes outside of biochemical recurrence, such as the risk of metastases and cancer-specific death.[6,7] Appropriate identification of patients at higher likelihood for such outcomes may provide an opportunity for therapeutic interventions to mitigate this risk.

2.2 Personalizing prognostic models in prostate cancer: The pre-metastatic niche.

The ‘seed-and-soil’ hypothesis was proposed by Paget in 1889, and suggests that the biological characteristics of certain tissues may foster invasion and growth of metastases.[8] Identification of these susceptible areas, termed pre-metastatic niches, has numerous potential clinical applications. For instance, patients with more abundant niches may have increased metastatic potential – niche prevalence could therefore serve as a personalized supplement to current prognostic models.[9] Alternatively, the pre-metastatic niche could act as a target of anticancer therapy, preventing metastases from developing. A necessary precursor to clinical use of the pre-metastatic niche is accurate molecular characterization of this entity. The seminal studies defining the composition of the pre-metastatic niche are described herein.

2.3 VEGFR1+ Bone Marrow Derived Cells (BMDCs) initiate the pre-metastatic niche.

Kaplan *et al* assessed mice injected with either LLC or B16 melanoma cells. While LLC cells have a predilection for pulmonary spread, B16 melanoma cells metastasize in a more widely disseminated fashion. At day 14 after tumor inoculation, it was observed that deposition and clustering of VEGFR1⁺ BMDCs occurred in terminal bronchioles prior to arrival of tumor cells. By day 23, tumor micrometastases were visible. Sites of BMDC clustering appeared to be tumor specific; while LLC cells deposited only in the lungs and liver, B16 cells deposited in a range of tissues, such as the lung, liver, testis and spleen. VEGFR1⁺ BMDCs recruited to pre-metastatic niche sites had increased expression of the fibronectin receptor VLA-4 (integrin $\alpha_4\beta_1$), implicating the role of fibronectin in BMDC clustering.

2.4 MDSC recruitment may represent an early event in pre-metastatic niche formation.

Amongst the VEGFR1⁺ BMDCs that populate the pre-metastatic niche, a proportion are MDSCs, characterized by a Gr-1⁺/MAC1⁺ immunophenotype.[9] Recent evidence suggests that MDSCs play a critical role in inhibition of the antitumor immune response.[13] The recruitment of MDSCs to tumor sites appears to be driven by Stat3,

and work done in Dr Hua Yu's laboratory at City of Hope institution suggests that Stat3 may further activate tumor angiogenesis, promoting a functional tumor micro-environment.[14] Thus, abrogation of Stat3-mediated MDSC recruitment to the pre-metastatic niche may reduce metastatic potential. As discussed in the subsequent section, therapy with a VEGF-TKI could potentially inhibit these Stat3-mediated effects.

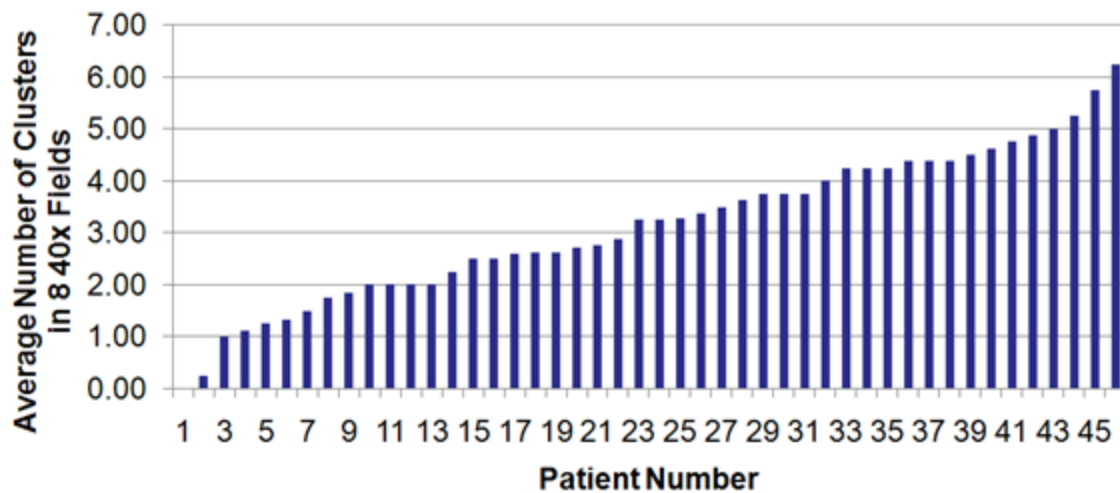
2.5 Preliminary Data: VEGF-TKI therapy decreases MDSC accumulation in tumor tissue.

Our external collaborator, Dr. Pal's group have previously reported a series of experiments in Renca-tumor bearing mice suggesting an antitumor effect of sunitinib that is Stat3 dependent.[15] Specifically, these studies demonstrate a reduction in Stat3 activation in MDSCs with sunitinib therapy. This reduction correlated with a decrease in expression of Stat3-mediated pro-angiogenic factors, such as VEGF and CXCL2 (the latter inhibits endothelial progenitor cell recruitment).[16] Furthermore, treatment with sunitinib decreased recruitment of MDSCs to tumor tissue.

2.6 Preliminary Data: The pre-metastatic niche is detectable in high-risk prostate cancer

To determine the role of the pre-metastatic niche in prostate cancer, a separate retrospective study, specifically examining the predictive role of the niche in the benign lymph nodes of men with high risk prostate cancer was undertaken. In COH IRB 09213, the City of Hope Prostate Cancer Database (COH Database) was used to identify 46 patients with high-risk PCa (baseline PSA > 20, pT3a-4 disease, or biopsy Gleason 8-10) who had undergone radical prostatectomy and pelvic lymph node dissection (PLND). The COH PCR prospectively collects clinical data associated with patients undergoing prostatectomy at the institution, and warehouses available clinical specimens. Benign tissue specimens (paraffin-embedded) derived from PLND were acquired for each patient, and were stained for VEGFR1 expression. VEGFR1+ cell clusters were counted within 8 distinct 40x fields, and the cluster count was averaged. The average cluster count was 3.13 (standard deviation, 1.43), and ranged from 0-6.25 (see Figure 1). VEGFR1+ clustering in PLND specimens was a significant predictor of biochemical recurrence on multivariate Cox proportional hazards analysis, and outperformed other variables including established prognostic factors such as age, extracapsular spread, seminal vesicle invasion, and the aforementioned high-risk features. Patients with increased VEGFR1+ clustering pelvic lymph node tissue had a shorter interval to biochemical recurrence (HR 0.18, P<0.10). These preliminary results indicate that increased VEGFR1+ cell clustering in benign nodal tissue may predict poorer clinical outcome in patients with high-risk PCa. This dataset is consistent with a recent report from Fujita *et al* (*Cancer Sci* 2009; 100(6):1047-50), which also suggested that VEGFR1 staining in pelvic lymph nodes predicted the risk of biochemical recurrence after radical prostatectomy in a more heterogeneous group. Together with this dataset, there is emerging rationale for examining VEGFR1 as a key component of the pre-metastatic niche.

Figure 1. Distribution of VEGFR1 clustering in the pelvic lymph nodes of 46 patients with lymph node negative prostate cancer who have been treated with definitive surgical intervention. The number of clusters visualized in 8 40x fields was averaged.



2.7 Preliminary Data: VEGF-TKIs have demonstrable efficacy in the setting of prostate cancer, and have been employed in neoadjuvant trials.

Data has emerged for the agent sunitinib in the setting of metastatic, hormone refractory prostate cancer. In one phase II study, patients who had received no prior cytotoxic therapy (Group A) or prior docetaxel therapy (Group B), (n=17 in each group), were treated with daily sunitinib.[17] One patient in each group had a documented PSA response. Furthermore, 7 and 8 patients had a stable PSA at 12 weeks in groups A and B, respectively. Interestingly, radiographic responses were observed in the absence of PSA responses. A separate phase II study assessed sunitinib specifically in the setting of docetaxel failure, and elicited similar response rates.[18] Preclinical studies have suggested potential synergy between sunitinib and docetaxel; this combined regimen is being further explored.[19,20] At least two studies have assessed sunitinib prior to prostatectomy.[21,22] An experience reported by the M.D. Anderson Cancer Center exploring three cycles of sunitinib (37.5 mg oral daily) prior to surgery enrolled a total of 44 patients.[22] Thus far, in 30 patients that have completed surgery, 1 CR has been reported. However, 3 patients were characterized as treatment failures (defined by unresectable pelvic nodal disease, confirmed post-operative PSA ≥ 0.2 ng/mL, or administration of post-operative radiation or ADT. Thus, while sunitinib appears to be relatively safe in the neoadjuvant setting (no grade 4 toxicities or toxicity-related discontinuations were observed), there may be rationale to explore more potent agents in this setting, such as axitinib.

2.8 Rationale for pazopanib therapy

Pazopanib (Novartis) has been chosen because it is a novel, orally available, small molecule tyrosine kinase inhibitor of VEGF receptor-1,-2,-3 and is already approved for treatment of metastatic renal cell carcinoma after favorable results in a randomized phase III trial[7].

3 DRUG INFORMATION

Pazopanib (Novartis) is a novel, orally available, small molecule tyrosine kinase inhibitor of VEGF receptor-1,-2,-3 and is already approved for treatment of metastatic renal cell carcinoma after favorable results in a randomized phase III trial [28]. Further detailed results from nonclinical studies, as well as additional physical and chemical characteristics of pazopanib are available in the Investigator's Brochure (IB) [29].

As of the clinical data cut-off date for the current IB, 09 September 2010, a total of 42 clinical studies have been performed or are in progress in adult subjects with cancer. These studies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), ovarian cancer, breast cancer, soft tissue sarcoma, cervical cancer, colorectal cancer, hepatocellular cancer, multiple myeloma, and glioma. As of the cutoff, over 6000 subjects have enrolled on these clinical studies. Data collected to date show that oral pazopanib is absorbed after administration and that pazopanib administration at 800mg daily dose is associated with a reasonable safety profile and encouraging efficacy in various oncology settings [29].

3.1 Adverse Reactions

The following safety data is from the Prescribing Information for pazopanib, revised April 2012 [30].

3.1.1 Clinical Trials Experience

Renal Cell Carcinoma:

The safety of pazopanib has been evaluated in 977 patients in the monotherapy trials which included 586 patients with RCC at the time of NDA submission. With a median duration of treatment of 7.4 months (range 0.1 to 27.6), the most commonly observed adverse reactions ($\geq 20\%$) in the 586 patients were diarrhea, hypertension, hair color change, nausea, fatigue, anorexia, and vomiting.

The data described below reflect the safety profile of pazopanib in 290 RCC patients who participated in a randomized, double-blind, placebo-controlled trial. The median duration of treatment was 7.4 months (range 0 to 23) for patients who received pazopanib and 3.8 months (range 0 to 22) for the placebo arm. Forty-two percent of patients on pazopanib required a dose interruption. Thirty-six percent of patients on pazopanib were dose reduced. Table 3.1 presents the most common adverse reactions occurring in $\geq 10\%$ of patients who received pazopanib.

Table 3.1. Adverse Reactions Occurring in > 10% of Patients with RCC who Received Pazopanib Adverse Reactions

	Pazopanib (N=290)			Placebo (N=145)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	%	%	%	%	%	%
Diarrhea	52	3	< 1	9	< 1	0
Hypertension	40	4	0	10	< 1	0
Hair color changes	38	< 1	0	3	0	0
Nausea	26	< 1	0	9	0	0
Anorexia	22	2	0	10	< 1	0
Vomiting	21	2	< 1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Abdominal pain	11	2	0	1	0	0
Headache	10	0	0	5	0	0
Neutropenia	34	1	< 1	6	0	0
Thrombocytopenia	32	< 1	< 1	5	0	< 1
Lymphocytopenia	31	4	< 1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	< 1	19	< 1	0
Glucose increased	41	< 1	0	33	1	0
Total bilirubin increased	36	3	< 1	10	1	< 1
Phosphorus decreased	34	4	0	11	0	0
Sodium decreased	31	4	1	24	4	0
Magnesium decreased	26	< 1	1	14	0	0
Glucose decreased	17	0	< 1	3	0	0

Soft Tissue Sarcoma:

The safety of pazopanib has been evaluated in 382 patients with advanced soft tissue sarcoma, with a median duration of treatment of 3.6 months (range 0 to 53). The most commonly observed adverse reactions ($\geq 20\%$) in the 382 patients were fatigue, diarrhea, nausea, decreased weight, hypertension, decreased appetite, vomiting, tumor pain, hair color changes, musculoskeletal pain, headache, dysgeusia, dyspnea, and skin hypopigmentation.

The data described below reflect the safety profile of pazopanib in 240 patients who participated in a randomized, double-blind, placebo-controlled trial of patients with soft tissue sarcoma. The median duration of treatment was 4.5 months (range 0 to 24) for patients who received pazopanib and 1.9 months (range 0 to 24) for the placebo arm. Fifty-eight percent of patients on pazopanib required a dose interruption. Thirty-eight percent of patients on pazopanib had their dose reduced. Fourteen percent of patients who received pazopanib discontinued therapy due to adverse reactions. Table 3 presents the most common adverse reactions occurring in $\geq 10\%$ of patients who received pazopanib.

Table 3.2: Adverse Reactions Occurring in $> 10\%$ of Patients with STS who Received Pazopanib Adverse Reactions

	Pazopanib (N=240)			Placebo (N=123)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	%	%	%	%	%	%
Fatigue	65	13	1	48	4	1
Diarrhea	59	5	0	15	1	0
Nausea	56	3	0	22	2	0
Weight decreased	48	4	0	15	0	0
Hypertension	42	7	0	6	0	0
Appetite decreased	40	6	0	19	0	0
Hair color changes	39	0	0	2	0	0
Vomiting	33	3	0	11	1	0
Tumor pain	29	8	0	21	7	2
Dysgeusia	28	0	0	3	0	0
Headache	23	1	0	8	0	0
Musculoskeletal pain	23	2	0	20	2	0
Myalgia	23	2	0	9	0	0
Gastrointestinal pain	23	3	0	9	4	0
Dyspnea	20	5	< 1	17	5	1

Exfoliative rash	18	< 1	0	9	0	0
Cough	17	< 1	0	12	< 1	0
Peripheral edema	14	2	0	9	2	0
Mucositis	12	2	0	2	0	0
Alopecia	12	0	0	1	0	0
Dizziness	11	1	0	4	0	0
Skin disorder	11	2	0	1	0	0
Skin hypopigmentation	11	0	0	0	0	0
Stomatitis	11	< 1	0	3	0	0
Chest pain	10	2	0	6	0	0

Other adverse reactions observed more commonly in patients treated with pazopanib that occurred in $\geq 5\%$ of patients and at an incidence of more than 2% difference from placebo included insomnia (9% versus 6%), hypothyroidism (8% versus 0), dysphonia (8% versus 2%), epistaxis (8% versus 2%), left ventricular dysfunction (8% versus 4%), dyspepsia (7% versus 2%), dry skin (6% versus <1%), chills (5% versus 1%), vision blurred (5% versus 2%), and nail disorder (5% versus 0%).

Table 3.3 presents the most common laboratory abnormalities occurring in >10% of patients who received pazopanib and more commonly ($\geq 5\%$) in patients who received pazopanib versus placebo.

Table 3.3: Selected Laboratory Abnormalities Occurring in > 10% of Patients with STS who Received Pazopanib and More Commonly (> 5%) in Patients who Received Pazopanib versus Placebo Parameters

	Pazopanib(N=240)			Placebo (N=123)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	%	%	%	%	%	%
Hematologic						
Leukopenia	44	1	0	15	0	0
Lymphocytopenia	43	10	0	36	9	2
Thrombocytopenia	36	3	1	6	0	0
Neutropenia	33	4	0	7	0	0
Chemistry						
AST increased	51	5	3	22	2	0

ALT increased	46	8	2	18	2	1
Glucose increased	45	< 1	0	35	2	0
Albumin decreased	34	1	0	21	0	0
Alkaline phosphatase increased	32	3	0	23	1	0
Sodium decreased	31	4	0	20	3	0
Total bilirubin increased	29	1	0	7	2	0
Potassium increased	16	1	0	11	0	0

Diarrhea: Diarrhea occurred frequently and was predominantly mild to moderate in severity in both the RCC and STS clinical trials. Patients should be advised how to manage mild diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact.

Lipase Elevations: In a single-arm RCC trial, increases in lipase values were observed for 27% (48/181) of patients. Elevations in lipase as an adverse reaction were reported for 4% (10/225) of patients and were Grade 3 for 6 patients and Grade 4 for 1 patient. In the RCC trials of pazopanib, clinical pancreatitis was observed in <1% (4/586) of patients.

Pneumothorax: Two of 290 patients treated with pazopanib and no patient on the placebo arm in the randomized RCC trial developed a pneumothorax. In the randomized trial of pazopanib for the treatment of STS, pneumothorax occurred in 3% (8/240) of patients treated with pazopanib and in no patients on the placebo arm.

3.1.2 Post marketing Experience

Potentially serious adverse reactions with pazopanib during post market experience included the following [8]:

- Hepatic effects: Cases of hepatic failure (including fatalities) have been reported during the use of pazopanib. In clinical trials with pazopanib, increase in serum transaminases (ALT, AST) and bilirubin were observed. In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin. The vast majority (92.5%) of all transaminase elevations of any grade occurred in the first 18 weeks.

- Hypertension: In clinical studies with pazopanib, events of hypertension including hypertensive crisis have occurred. Hypertension (systolic blood pressure ≥ 150 or diastolic blood pressure ≥ 100 mm Hg) occurs early in the course of treatment (39% of cases occurred by Day 9 and 88% of cases occurred in the first 18 weeks).
- QT Prolongation and Torsade de Pointes: In clinical studies with pazopanib, events of QT prolongation or Torsade de Pointes have occurred.
- Arterial Thrombotic Events: In clinical studies with pazopanib, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed. Fatal events have been observed. Pazopanib has not been studied in patients who have had an event within the previous 6 months.
- Haemorrhagic Events: In clinical studies with pazopanib haemorrhagic events have been reported. Fatal haemorrhagic events have occurred. Pazopanib has not been studied in patients who had a history of haemoptysis, cerebral, or clinically significant gastrointestinal haemorrhage in the past 6 months.
- Gastrointestinal Perforations and Fistula: In clinical studies with pazopanib, events of gastrointestinal (GI) perforation or fistula have occurred. Fatal perforation events have occurred.
- Wound Healing: No formal studies on the effect of pazopanib on wound healing have been conducted. Vascular Endothelial Growth Factor (VEGF) inhibitors may impair wound healing. The decision to resume pazopanib after surgery should be based on clinical judgment of adequate wound healing. Pazopanib should be discontinued in patients with wound dehiscence.
- Hypothyroidism: In clinical studies with pazopanib, events of hypothyroidism have occurred.
- Proteinuria: In clinical studies with pazopanib, proteinuria has been reported.

4 STUDY DESIGN

4.1 Description

This is a phase II, prospective, randomized, double blind (investigator and study subject will be blinded to treatment assignment; Investigational Pharmacy will be un-blinded) placebo controlled, two arm study. This study will assess biomarkers in post treatment samples (surgically resected lymph nodes) in the pazopanib group and placebo group. The objective is to compare the post treatment VEGFR1 (and other biomarker) levels between treatment and placebo groups. We also plan to compare these levels with those reported in previous

studies [4, 5]. This study will also assess progression free survival for a total of 2 years post prostatectomy.

4.2 Number of Patients

Approximately 30 patients will be enrolled in the study. 15 patients will be enrolled onto the treatment arm, and 15 patients will be enrolled to the placebo arm.

4.3 Number of Study Centers

This is a single-center study to be conducted at Huntsman Cancer Institute.

4.4 Duration

Enrollment is expected to be completed within 14 months. Patients will remain on study for 2 months. Subjects will be treated with either pazopanib or a placebo for 28 days until 2-7 days prior to radical prostatectomy. Post-surgery, subjects be followed for progression free survival for two years.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with signature in the patient research chart.

Patient No. _____

Patient's Initials: (L,F,M) _____

5.1 Inclusion Criteria

Yes/No (Response of "no" = patient ineligible)

5.1.1 _____ Men \geq 18 years of age

5.1.2 _____ Histological documentation of adenocarcinoma of the prostate, with available biopsy pathology. Biopsy material must be available for pathologic review.

5.1.3 _____ All patients must meet one or more of the following disease features: clinical stage \geq T3; Primary Gleason score of 4 **OR** Gleason score of 8, 9 or 10; serum PSA \geq 20 ng/mL; Prostate MRI findings consistent with T3 disease; Any clinical stage and PSA $>$ 10 and Gleason score 7; A Kattan nomogram predicted probability of being free from biochemical progression at 5 years after surgery of $<$ 60%.

5.1.4 _____ Patients must have a PSA \geq 2 ng/mL at the time of diagnosis of prostate cancer or later.

5.1.5 _____ No prior radiation or chemotherapy for prostate cancer treatment.

- 5.1.6 _____ Scheduled for radical prostatectomy surgery.
- 5.1.7 _____ ECOG Performance Status of 0 or 1.
- 5.1.8 _____ Patients may have been treated with up to 4 months of androgen deprivation therapy.
- 5.1.9 _____ No clinical evidence of metastatic prostate cancer, or enlarged pelvic lymph nodes in the imaging studies.
- 5.1.10 _____ Resected lymph nodes must be provided for all subjects for biomarker analysis immediately (same day) after surgery (radical prostatectomy).
- 5.1.11 _____ Adequate organ system function as defined by Table 5

Table 5: Definitions of Adequate Organ Function:

System	Laboratory Values
Hematology	
Absolute neutrophil count (ANC)	$\geq 1.5 \times 10^9/\text{L}$
Hemoglobin ^a	$\geq 9 \text{ g/dL}$ (5.6 mmol/L)
Platelets	$\geq 100 \times 10^9/\text{L}$
Prothrombin time (PT) or international normalized ratio (INR)	$\leq 1.2 \times \text{ULN}$
Activated partial thromboplastin time (aPTT)	$\leq 1.2 \times \text{ULN}$
Hepatic	
Total bilirubin	$\leq 1.5 \times \text{ULN}$
Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST)	Below the institutional upper limits of normal
Renal	
Serum creatinine	$\leq 1.5 \text{ mg/dL}$ (133 $\mu\text{mol/L}$)
Or, if $>1.5 \text{ mg/dL}$: Calculated creatinine clearance (Cl_{CR}) (reference appropriate appendix)	$\geq 30 \text{ mL/min}$ to $\geq 50 \text{ mL/min}$
Urine Protein to Creatinine Ratio (UPC; refer to Appendix A) ^b	<1
Or, 24-hour urine protein	$<1\text{g}$

- a. Subjects may not have had a transfusion within 7 days of screening assessment.

-
- b. If UPC ≥ 1 , then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value < 1 g to be eligible.

5.1.12 _____ Subjects must provide written informed consent within one month prior to performance of study-specific procedures or assessments and must be willing to comply with treatment and follow up.

Note: Informed consent will be obtained after establishing the diagnosis of high risk, localized prostate cancer, and may be obtained prior to start of the specified screening window.

Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study such as bone scan) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol

5.2 Exclusion Criteria

Yes/No (Response of "yes" = patient ineligible)

5.2.1 _____ Clinical evidence of metastatic prostate cancer.

5.2.2 _____ Prior malignancy. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.

5.2.3 _____ Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to: Active peptic ulcer disease, Known intraluminal metastatic lesion/s with risk of bleeding, Inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease), or other gastrointestinal conditions with increased risk of perforation, History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment.

5.2.4 _____ Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to:

- Malabsorption syndrome or
- Major resection of the stomach or small bowel.

5.2.5 _____ Corrected QT interval (QTc) > 480 msec

Note: Correction method should be reported

5.2.6 _____ History of any one or more of the following cardiovascular

conditions within the past 6 months:

- Cardiac angioplasty or stenting
- Myocardial infarction
- Unstable angina
- Coronary artery bypass graft surgery
- Symptomatic peripheral vascular disease
- Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) (See Appendix C for description)

5.2.7 _____ No evidence of preexisting uncontrolled hypertension. If the patient has a history of or elevated blood pressure at baseline then they must have controlled hypertension documented and confirmed by 2 consecutive blood pressure readings taken within 1 hour. The baseline systolic blood pressure readings must be ≤ 140 mm Hg, and the baseline diastolic blood pressure readings must be ≤ 90 mm Hg.

Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Following antihypertensive medication initiation or adjustment, blood pressure (BP) must be re-assessed three times at approximately 2-minute intervals. At least 24 hours must have elapsed between anti-hypertensive medication initiation or adjustment and BP measurement. These three values should be averaged to obtain the mean diastolic blood pressure and the mean systolic blood pressure. The mean SBP / DBP ratio must be $<140/90$ mmHg (OR $150/90$ mmHg, if this criterion is approved by the HCI DSMC Chair or Co-chair) in order for a subject to be eligible for the study (see Table 7.1 for details on BP control and re-assessment prior to study enrollment).

5.2.8 _____ History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.

5.2.9 _____ Major surgery or trauma within 28 days prior to first dose of investigational product and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major surgery).

5.2.10 _____ Evidence of active bleeding or bleeding diathesis.

5.2.11 _____ Patients on active therapeutic anticoagulation.

5.2.12 _____ Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage

Note: Lesions infiltrating major pulmonary vessels (contiguous tumour and vessels) are excluded; however, the presence of a tumor that is

touching, but not infiltrating (abutting) the vessels is acceptable (CT with contrast is strongly recommended to evaluate such lesions).

- Large protruding endobronchial lesions in the main or lobar bronchi are excluded; however, endobronchial lesions in the segmented bronchi are allowed.
- Lesions extensively infiltrating the main or lobar bronchi are excluded; however, minor infiltrations in the wall of the bronchi are allowed.

5.2.13 _____ Recent hemoptysis ($\geq \frac{1}{2}$ teaspoon of red blood within 8 weeks before first dose of study drug).

5.2.14 _____ Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures.

5.2.15 _____ Unable or unwilling to discontinue use of prohibited medications listed in Section 6.3.5 for at least 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study.

5.2.16 _____ Treatment with any of the following anti-cancer therapies:

- radiation therapy, chemotherapy, immunotherapy, biologic therapy, investigational therapy
- surgery or tumor embolization within 14 days prior to the first dose of pazopanib OR
- hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of Pazopanib

5.2.17 _____ Administration of any non-oncologic investigational drug within 30 days or 5 half lives whichever is longer prior to receiving the first

5.2.18 _____ Any ongoing toxicity from prior hormonal therapy that is >Grade 1 and/or that is progressing in severity

5.2.19 _____ Known active viral infection.

- Note: Viral hepatitis testing is required at screening for all patients

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

PI Signature

Date

Time

6 TREATMENT PLAN

Treatment will be administered in an outpatient setting. Randomization will take place by the Investigational Pharmacy at Huntsman Cancer Institute. Patients who are enrolled will be randomized to either pazopanib experimental arm, or the placebo arm. Patients will take either 800 mg pazopanib or a placebo tablet orally for 28 days of therapy.

The initiation of pazopanib or placebo will be contingent upon the date selected for radical prostatectomy and pelvic lymph node dissection, with 28 days of planned therapy to conclude at least 48 hours prior to surgical intervention.

6.1 Administration Schedule

Treatment Arm:

Pazopanib 800 mg orally daily for 28 days prior to radical prostatectomy.

Placebo Arm:

Placebo, orally, daily for 28 days prior to radical prostatectomy

One cycle = 28 days

Only one cycle of pazopanib or placebo will be instituted for this protocol.

Surgery

Radical prostatectomy with pelvis lymph node dissection will be performed as standard of care after ~ 7 days of completion of the 28 days of treatment with either pazopanib or placebo. A 48 hour washout period from treatment is required prior to surgery. Prostatectomy may be performed via any accepted methodology (open, laparoscopic, robotic-assisted, etc.). Notably, standard wait times for prostatectomy at Huntsman Cancer Institute vary between 5-6 weeks from the time of seeing the surgeon for prostatectomy. Thus, it is not anticipated that the current protocol will delay standard of care therapies on the control or experimental arms. Surgery will not be delayed longer than 8 weeks from the time of randomization.

6.2 Pazopanib/Placebo Treatment

6.2.1 How Supplied, Stored, Packaged and Labeled

Pazopanib tablets are manufactured and provided by Novartis. The tablets are supplied as 50 mg, 100 mg, 200 mg, 400 mg and 500 mg (as free base) tablets for oral administration to support oncology indications. The 200 mg and 400 mg tablets are oval-shaped white tablets and will be used for this purpose of this study.

Placebo tablets will match the oval-shaped 200 mg and 400 mg tablets and will also be provided by Novartis.

All tablets will be packaged in white high density polyethylene (HDPE) bottles with white plastic, induction seal, child-resistant caps.

Huntsman Cancer Institute Investigational Pharmacy will randomize patients to either arm.

6.2.2 Preparation and Administration

800 mg (2x400mg or 4x200mg) Pazopanib per day should be taken orally without food at least one hour before or two hours after a meal.

Placebo tablets should also be taken orally without food at least one hour before or two hours after a meal.

Patients should be instructed NOT to crush tablets. The consumption of crushed pazopanib tablets leads to increases in the extent of oral absorption and may result in increased toxicities.

6.2.3 Accountability and Compliance

Patients will be instructed to keep a diary of daily medication compliance. The study team will collect the diary at the completion of 28 days of pazopanib/placebo treatment prior to radical prostatectomy.

6.3 Concomitant Medications

All subjects will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the 4 weeks prior to Screening. The investigator must be informed as soon as possible about any new medication(s) taken from the time of Screening until the completion of the post-treatment follow-up visit.

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate.

Anti-emetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT antagonists) may be administered prophylactically in the event of nausea. Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea. Although acetaminophen at doses of ≤ 2 g/day is permitted, it should be used with caution in subjects with impaired liver function.

6.3.1 Permitted Medications – Use with Caution

Specific recommendations regarding anticoagulants:

Subjects taking concomitant anticoagulant therapy at “**baseline**” are excluded from the study. Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib has no effect on the metabolism of S-warfarin. Hemorrhagic events, however, have been reported in clinical studies with pazopanib; therefore, pazopanib should be used with caution in subjects with increased risk of severe bleeding or who are receiving concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin). Therefore, patients may only be on concomitant anticoagulant therapy if such therapy is deemed necessary by the investigator “**after**” study commencement and is monitored closely while on study treatment.

6.3.2 Specific recommendations regarding hypoglycemic therapy including insulin:

Results from drug-drug interaction studies conducted in subjects with cancer suggest that there will be no clinically relevant pharmacokinetic interaction between pazopanib and hypoglycemic agents. Transient decreases in serum glucose (mainly Grade 1 and 2, rarely Grade 3) have been observed in clinical studies with pazopanib. In addition, decreases in blood sugar have been recently reported in subjects treated with another small molecule tyrosine kinase inhibitor, sunitinib [10]. Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.

6.3.3 The Effects of Pazopanib on Other Drugs

In vitro data indicate that pazopanib is a potential inhibitor for CYP3A4, CYP2C8, CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2A6, CYP2B6, and CYP2E1. Pregnane X receptor transient transfection assay suggested some potential for human CYP3A4 induction at high concentrations. Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 *in vivo*, but had no clinically relevant effect on CYP1A2, CYP2C9 or CYP2C19 metabolism. Therefore, concomitant use of pazopanib with certain medications (substrates of CYP3A4, CYP2C8, and CYP2D6) with a narrow therapeutic window should be undertaken with **CAUTION** due to the potential for alterations in the pharmacologic effects of these medications or an increased risk for serious or life threatening adverse events associated with such medications (see below) secondary to the inhibition of specific CYP enzymes by pazopanib. In addition, the potential for drug interaction with such medications, although diminished, may persist after the last dose of pazopanib due to its long half-life (i.e., mean 30.9 hours); therefore, continue to exercise **CAUTION** for at least 7 days and up to 15 days after the last dose of pazopanib when administering these medications. These medications include (but are not limited to):

- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that includes severe vasospasm leading to peripheral as well as cerebral ischemia)
- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidine, propafenone (potential increased risk for QT interval prolongation and Torsade de Pointes)
- Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

6.3.4 **The Effects of Other Drugs on Pazopanib**

Results from *in vitro* studies suggest that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Furthermore, *in vitro* data suggest that pazopanib is a substrate for p-glycoprotein. Substances that induce or inhibit CYP3A4 may alter the pharmacologic effects of pazopanib and should be used with **CAUTION**.

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations. Co-administration of strong CYP3A4 inhibitors is prohibited (see Section on Prohibited Medications); therefore selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended.

CYP3A4 inducers may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. **Drugs that induce CYP3A4 and may decrease pazopanib plasma concentrations include (but are not limited to):**

- Glucocorticoids: cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)
- Anticonvulsants: phenytoin, carbamazepine, phenobarbital, oxcarbazepine
- HIV antivirals: efavirenz, nevirapine
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentene
- Miscellaneous: St. John's Wort, modafinil, pioglitazone

6.3.5 **Prohibited Medications**

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations; therefore, co-administration of strong CYP3A4 inhibitors is **PROHIBITED** beginning **14** days prior to the first dose of study drug until discontinuation from the study. **Strong CYP3A4 inhibitors include (but are not limited to):**

- Antibiotics: clarithromycin, telithromycin, troleandomycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, lopinavir)
- Antifungals: itraconazole, ketoconazole, voriconazole
- Antidepressants: nefazodone

Subjects should not receive other anti-cancer therapy [cytotoxic, biologic, radiation, or hormonal] while on treatment in this study.

HMG-CoA Reductase Inhibitors (Statins) should be held during the treatment period and for one week after discontinuation to lower the risk for liver toxicity.

Subjects taking concomitant anticoagulant therapy at baseline are excluded from the study.

Drugs with known risk to induce torsades de pointes or prolong QT interval (refer to appendix B for a comprehensive list). Drugs that have a possible risk of prolonging QT interval should be used with caution.

Subjects should not receive any other investigational drug within 15 days of the last dose of pazopanib and until post-treatment blood draws are completed.

Patients will be strongly discouraged from drinking alcohol during the treatment period.

6.4 Duration of Therapy

Patients will be randomized to either the pazopanib arm or the placebo arm. The duration of patient treatment will be 28 days until 2-7 days prior to radical prostatectomy. Post-prostatectomy patients will be followed as per standard of care for ≥ 30 days to assess for post-operative complications. Study treatment will be discontinued after one cycle or 28 days of treatment. Patients will be removed from study after their 30 day post radical prostatectomy follow-up visit. Patients may also be removed from study for any of the following: intolerable toxicities, patient withdrawal, or PI decision.

If a patient misses more than 7 consecutive days of study treatment they may be replaced at the discretion of the investigator. Patients who are unable to have surgery will be considered not evaluable and will be replaced.

Following prostatectomy, patients will be followed clinically for progression for a maximum of two years. PFS is defined in Section 10.2.

7 TOXICITIES AND DOSEAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for adverse event and serious adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded: (<http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx>).

7.1 Dose Modifications

The investigator should determine if an adverse event is related to study treatment, which is defined as possibly, probably, or definitely related to pazopanib. If an adverse event is considered at least possibly related to pazopanib and requires a dose modification as described in this section, treatment will be un-blinded and the necessary dose modifications will be utilized. Adverse events that are not related to pazopanib will be defined as unlikely related and unrelated.

As a general rule, if dose reduction of pazopanib is necessary, the dose should be reduced stepwise by 200 mg at each step, and the subject should be monitored for approximately 10 to 14 days at each dose level. If toxicity does not abate during this monitoring time, the pazopanib may need to be interrupted and/or the dose further decreased with continued monitoring for an additional 10-14 days at each dose level, and so on.

If the toxicity has abated with reduction of the dose and dose re-escalation is considered safe by the investigator, the pazopanib dose can then be increased step-wise back to the pre-event dose (in 200 mg increments, after monitoring for 10-14 days at each dose level to ensure that toxicity did not recur or worsen).

Subjects will be permanently discontinued from treatment for the following:

- a. Grade \geq 2 adverse events attributed by the investigator as related to pazopanib, and which do not resolve within 7 days after dose modification of pazopanib.
- b. Grade \geq 2 thrombocytopenia regardless of attribution
- c. Grade \geq 2 elevations in ALT or AST regardless of attribution
- d. Patients with toxicity that requires dose interruption for >7 days will be taken off treatment to avoid delaying curative surgery
- e. Any grade 3 or higher adverse event
- f. Any newly diagnosed DVT or PE or arterial thrombotic event

Table 7.1 Dose Modification Algorithms for Potential Treatment-Related Adverse Events

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	

AE Terms & Descriptions	Dose Modification Algorithms
Grade 2 Asymptomatic and persistent SBP of ≥ 140 and < 170 mmHg, or DBP ≥ 90 and < 110 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg).	<p>Step 1. If the event is attributed by the investigator as related to pazopanib, decrease the dose of pazopanib by 200 mg.</p> <p>Step 2. Adjust current or initiate new antihypertensive medication(s).</p> <p>Step 3. Titrate antihypertensive medication(s) during next 7 days as indicated to achieve well-controlled^a blood pressure (BP). If BP is not well-controlled within 7 days, discontinue treatment and consider referral to a specialist.</p>
Grade 3 Asymptomatic SBP ≥ 170 mmHg, or DBP ≥ 110 mmHg, or failure to achieve well-controlled BP within 7 days.	Discontinue pazopanib and continue follow-up per protocol.
Grade 4 or Refractory hypertension unresponsive to above interventions.	Discontinue pazopanib and continue follow-up per protocol.
Prolongation of QTc Interval: If the QTc is prolonged, the ECG should be manually read to ensure accuracy of the reading. The values below refer to manually-read ECGs. REFER READER TO ECG SECTION IN PROTOCOL	
Grade 2: QTc $\geq 481 - 500$ msec	If the event is attributed by the investigator as related to pazopanib, decrease pazopanib by 200 mg ; monitor as clinically indicated. If the event resolves to grade 1 or baseline in 7 days or less, continue pazopanib at the reduced dose. Repeat EKG in 7 days, if the event persists, discontinue pazopanib.
Grade 3 or higher: QTc ≥ 501 msec	Discontinue pazopanib and continue follow-up per protocol.
Proteinuria	
UPC < 3	Continue pazopanib at the current dose; monitor as clinically indicated
UPC ≥ 3 or 24-h urine protein ≥ 3 g	<p>Step 1. Interrupt pazopanib.</p> <p>Step 2. Repeat UPC or 24-hr urine protein monitoring until UPC is < 3 or 24-hr urine protein is < 3 grams. If the event resolves in 7 days or less, then restart pazopanib dose-reduced by 200 mg.</p> <p>Step 3. If UPC ≥ 3 or 24-h urine protein ≥ 3g recurs, repeat steps 1 and 2.</p> <p>Step 4. If UPC ≥ 3 or 24-hr urine protein ≥ 3 recurs and the pazopanib dose can no longer be reduced, discontinue pazopanib and continue follow-up per protocol.</p>
Hemorrhage /Bleeding: Investigate and document underlying etiology of the bleeding	
Grade 1	<p>For hemoptysis, interrupt pazopanib and contact the Novartis Study Physician to discuss whether further treatment with pazopanib is appropriate.</p> <p>For other Grade I hemorrhage/bleeding events, continue pazopanib at the current dose; monitor as clinically indicated.</p>

AE Terms & Descriptions	Dose Modification Algorithms
Grade 2	Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue pazopanib and continue follow-up per protocol.
Grade 3 or 4, or Recurrent \geq Grade 2 event after dose interruption/reduction.	Discontinue pazopanib and continue with follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Any Grade	Discontinue pazopanib and continue follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Discontinue pazopanib and continue follow-up per protocol.
Thrombocytopenia: Investigate and document underlying cause	
Grade 1	Continue pazopanib with current dose; monitor as clinically indicated.
Grade ≥ 2	Discontinue pazopanib and continue with follow-up per protocol.
Anemia: No specific dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above.	
Palmar-plantar Erythrodysesthesia Syndrome	
Grade 1 Minimal skin changes or dermatitis without pain (erythema, oedema, hyperkeratosis)	1. Continue pazopanib at present dose
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (ADLs) (peeling, blisters, oedema, bleed, hyperkeratosis)	1. Hold pazopanib 2. Treat as clinically appropriate 3. If resolution to grade 1 or better in 7 days or less, restart pazopanib with a dose reduction by 200 mg. 4. If recurrent consider a further dose reduction to 200mg or discontinuation
Grade 3 Severe skin changes with pain and limiting self care ADLs	1. Discontinue pazopanib
Other Clinically Significant Adverse Events^b	
Grade 1	Continue pazopanib; monitor as clinically indicated.
Grade 2	The investigator will attribute whether the adverse event is attributed to pazopanib. If the event is related to pazopanib,

AE Terms & Descriptions	Dose Modification Algorithms
	decrease the dose of pazopanib by 200 mg, and if the event resolves in 7 days or less, continue at the decreased dose. If the event does not resolve after 7 days, discontinue treatment with pazopanib. If the event is attributed by the investigator as unrelated to pazopanib, continue pazopanib and monitor as clinically indicated.
Grade 3 or 4	Discontinue pazopanib and continue follow-up per protocol.

- Well-controlled BP defined as SBP <140 mmHg and mean DBP <90 mmHg.
 - AEs are graded according to NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4)
- Abbreviations: BP, blood pressure;

7.1.1 Dose Modifications and Management of Liver toxicity

Dose modifications for pazopanib in case of liver-related treatment-emergent AEs are provided in Table 7.2. As a general rule, since many subjects are taking multiple concurrent medications, it is critical to (a) do a thorough evaluation of the subject's concurrent medications and (b) identify and discontinue those with known hepatotoxicity and replace with a non-hepatotoxic equivalent for the same indication if necessary. Liver dysfunction must be fully evaluated even if clinical signs and symptoms indicate progression of liver tumor lesions. Imaging studies must be obtained to document potential progression of malignancy.

Table 7.2 Management of Treatment Emergent Hepatotoxicity

Event	Dose Modification Algorithms
Grade 1 ALT or AST: > ULN – 3.0 x ULN	Continue pazopanib at current dose and monitor LFTs closely. .
Grade 2 ALT or AST elevation (>3.0 x ULN)	Permanently discontinue treatment with pazopanib, monitor the patient closely until LFTs resolve to baseline or grade 1.
Grade 2 AST or ALT elevation in the setting of bilirubin elevation greater than 2.0 ULN	Permanently discontinue treatment with pazopanib, monitor closely until LFTs resolve to baseline or grade 1.
Grade 3 or higher AST or ALT elevation (>5.0 x ULN)	Permanently discontinue treatment with pazopanib, monitor closely until LFTs resolve to baseline or grade 1.

7.2 Supportive Care

- ### 7.2.1
- All supportive measures consistent with optimal patient care will be given throughout the study.

8 STUDY CALENDAR^a

	Screening ^a	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5 (surgery)	Week 9(1 month Post- Surgery) ⁱ	Post Study Assessments ^j
Informed Consent	X							
History/Progress Notes	X							
Concomitant Medications	X	X	X	X	X			
Physical Exam	X	X			X		X	
Vitals signs	X ^l	X	X ^b		X		X	
ECOG Performance Status	X	X			X		X	
Safety Assessments			X	X	X	X	X	
CBC ^c	X	X			X		X	
CMP ^d	X	X	X	X	X		X	
UPC ^k	X				X		X	
TSH, Free T4 ^e	X				X			
Coagulation test	X							
PSA	X						X	X
Viral Hepatitis Panel ^f	X							
EKG	X					X		
CT or MRI scan ^g	X							
Bone scan ^g	X							
Pazopanib or Placebo		X	X	X	X			
Prostatectomy/ PLND						X		
Collection of Tumor specimens						X		

^aALL Pre-study/Screening procedures should be completed within 28 days, with the exception of CT or MRI scan which need to be performed within 8 weeks prior to study enrollment and laboratory tests which need to be completed within 2 weeks prior to study enrollment. Week 1 laboratory assessments do not need to be repeated if screening labs were performed within 7 days of Week 1 Day 1. The week 1 physical exam, vitals and ECOG do not need to be repeated if done within 15 days of week 1 day 1, unless determined clinically indicated per treating physician.

^bMonitoring of BP only: A measurement of BP should be taken at day 7+/- 3 days. BP can be assessed by any method (i.e., at home or by another physician) as long as the study physician is informed of the measurement, verifies any measurement that is not normal and takes appropriate action.

^cCBC with differential and platelets. Permanently discontinue pazopanib for any grade ≥ 2 thrombocytopenia

^dCMP includes Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, Urea Nitrogen. If clinically indicated, correction of electrolytes (most importantly, potassium, magnesium and calcium) to within normal ranges should take place prior to study entry and during study conduct as standard of care. Permanently discontinue pazopanib for grade ≥ 2 elevation of AST or ALT.

- ^e TSH and free T4 laboratory assessment will be repeated at week 4 only if the patient shows clinical signs of abnormal thyroid function tests at screening
- ^f All patients must be screened for Viral Hepatitis. These laboratory assessments include the following: Hepatitis A Virus Antibody, Hepatitis B Virus Core Antibody, and Hepatitis C Virus Antibody.
- ^g Axial imaging of the pelvis (either by CT or MRI) will be done as part of preoperative staging evaluation. A bone scan will be done if clinically indicated per investigator discretion.
- ^h All visits have a +/- 3 day window, with the exception of the prostatectomy/PLND which must be performed within 2 – 7 days of the completion of 28 days of treatment. Prostatectomy must be completed no later than 8 weeks post randomization.
- ⁱ The post-surgery visit will occur per standard of care practices but should occur ≥ 30 days after surgery to assess for any post-operative complications
- ^j Patients will be followed as standard of care until progression in PSA levels ≥ 0.2 ng/mL for two years post prostatectomy
- ^k For the baseline UPC: If UPC ≥ 1 , then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value < 1 g to be eligible. At the four week visit, a UPC must be done to assess for proteinuria.
- ^l If the subject has a history of or elevated blood pressure ($> 140/90$ mmHg) at baseline, 2 consecutive blood pressure readings should be done within 1 hour to confirm eligibility. Please refer to exclusion criteria 5.2.7.

9 STUDY PROCEDURES

Screening:

- Informed Consent
- Physical exam
- Review of medical history/baseline symptoms
- Vital Signs- If the subject has a history of or elevated blood pressure ($> 140/90$ mmHg) at baseline, 2 consecutive blood pressure readings should be done within 1 hour to confirm eligibility.
- Concomitant Medication Assessment
- ECOG Performance status
- Labs to be performed within two weeks prior to enrollment:
 - o CBC w/diff
 - o CMP – Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen
 - o Coagulation test – PT, PTT, INR
 - o PSA
 - o Thyroid function – TSH, Free T4
 - o UPC: If $UPC \geq 1$, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1 g to be eligible.
 - o Viral Hepatitis Panel: Hepatitis A Virus Antibody, Hepatitis B Virus Core Antibody, and Hepatitis C Virus Antibody.
- CT or MRI of the pelvis to evaluate disease to be completed within 8 weeks of enrollment
- Bone Scan, if clinically indicated, to evaluate disease to be completed within 8 weeks of enrollment
- EKG
- Verification of an operative date for prostatectomy/pelvic lymph node dissection that allows for the 28 day therapeutic period as well as a 48 hour washout period prior to surgery. Prostatectomy may be performed via any accepted methodology (open, laparoscopic, robotic-assisted, etc.).

Week 1 (Day 1):

- Physical Exam-if clinically indicated per investigator discretion. Not required if screening physical was done within 15 days of Week 1 Day 1.
- ECOG Performance Status. Not required if done within 15 days of Week 1 Day 1.
- Vital Signs. Not required if done within 15 days of Week 1 Day 1.
- Labs: (do not need to be repeated if screening labs performed within 7 days of W1D1)
 - o CBC w/diff
 - o CMP – Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide,

Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen

- Safety Assessment: Monitoring and recording all adverse events and serious
- Concomitant medication assessment
- Treatment with pazopanib or Placebo

Week 2 (Day 7 +/- 3 days):

- Vital Signs - Monitoring of BP only: A measurement of BP should be taken at day 7 +/- 3 days. BP can be assessed by any method (i.e., at home or by another physician) as long as the study physician is informed of the measurement, verifies any measurement that is not normal and takes appropriate action.
- CMP: Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen. *Permanently discontinue pazopanib for \geq grade 2 elevations in ALT, AST*
- Concomitant medication assessment
- Safety assessment - Monitoring and recording all adverse events and serious adverse events using the CTCAE version 4.
 - o Safety and Con/Med Assessments may be done over the phone.
- Treatment with pazopanib or Placebo

Week 3 (Day 15 +/- 3 days):

- Treatment with pazopanib or Placebo
- CMP: Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen: *Permanently discontinue pazopanib for \geq grade 2 elevations in ALT or AST.*
- Safety Assessments: Monitoring and recording all adverse events and serious.
 - o Safety and Con/Med Assessments may be done over the phone

Week 4 (Day 22 +/- 3 days):

- Physical Exam
- ECOG Performance Status
- Vitals
- Labs:
 - o CBC w/diff: *Permanently discontinue pazopanib for grade \geq 2 thrombocytopenia*
 - o CMP – Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen: *Permanently discontinue pazopanib for \geq grade 2 elevations of ALT or AST*
 - o TSH, Free T4: laboratory assessment will only be repeated at week 4 if the patient shows clinical signs of abnormal thyroid function tests at screening
 - o UPC evaluation

- Treatment with pazopanib daily or Placebo until Day 28. Medication Compliance must be documented.
- Concomitant Medication assessment
- Safety assessment - Monitoring and recording all adverse events and serious adverse events using the CTCAE version 4

Week 5: Day 30 – Day 37 (Surgery)

- EKG prior to surgery
- Prostatectomy with Pelvic Lymph Node Dissection: to be performed after the completion of 48hour washout period from treatment/placebo (NOTE: Surgery must not be delayed longer than 8 weeks from the time of randomization).
 - o Collection of benign lymph tissue samples from prostatectomy and pelvic lymph node dissection
 - o Refer to Section 14.1 for more details on collection, processing and storage

Week 9 (1 Month Post-op)

This visit will occur as standard of care, however should occur ≥ 30 days after surgery to assess all toxicities and post-surgery complications.

- Physical Exam
- ECOG Performance Status
- Labs:
 - o CBC w/diff
 - o CMP – Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen
 - o Urinalysis
 - o PSA
- Safety assessment - Monitoring and recording all adverse events and serious adverse events using the CTCAE version 4

Follow-up

- PSA will be performed as clinically indicated post prostatectomy for 2 years or until the development of biochemical metastatic recurrence.

10 CRITERIA FOR EVALUATION AND ENDPOINT

10.1 Assessment of the pre-metastatic niche

Normal lymph node tissue will be assessed for pre-metastatic niche density, characterized as the average number of VEGFR1-positive clusters in 8 distinct 40x microscopic fields. This assessment will be performed through previously defined techniques at City of Hope Medical Center.

10.2 Assessment of BMDCs and MDSCs

Normal lymph node tissue will also be assessed by flow cytometry for the number of bone marrow derived cells (BMDCs) as well as myeloid derived suppressor cells (MDSCs) and Tregs.

10.3 Time to Biochemical Recurrence

Progression Free Survival will use the time to biochemical recurrence which is defined as the number of days elapsed between prostatectomy and the first recording of a PSA value ≥ 0.2 ng/mL. Patients will be followed for progression free survival for two years.

10.4 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate and temperature) will be obtained in the sitting position. Patients should be sitting for 3-5 minutes prior to obtaining vital signs.

Safety Laboratory Determinations

Laboratory assessments should be performed as indicated in Section 8 and 9: Study Calendar and Procedures. These assessments may be carried out within 3 days before the actual visit to allow flexibility in scheduling. Assessments may be performed more frequently if clinically indicated. Correction of electrolytes (most importantly, potassium, magnesium and calcium) to within normal ranges should take place prior to study entry and during study conduct as clinically indicated.

All laboratory tests with values that become abnormal and clinically significant while the subject is participating in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal or baseline. See Section 7 for guidance on subject follow-up and dose management in response to specific laboratory abnormalities.

Table 10.3.1 shows the clinical laboratory assessments that should be reported.

Table 10.3.1 Clinical Laboratory Assessments

Clinical Chemistry	
Renal function	Urea, Creatinine ^a
Liver function test (LFT) Panel	Albumin, Alkaline phosphatase, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Bilirubin (total) ^b
Electrolytes and others	Calcium, Potassium, Sodium, Magnesium, Inorganic phosphate, Glucose, and Lactate Dehydrogenase (LDH)
Hematology	Hematocrit, Hemoglobin, White Blood Cell Count, Red Blood Cell Count, Neutrophils, and Platelets
Coagulation Tests	Activated partial thromboplastin (aPTT) and International Normalization Ratio (INR) ^c
Urinalysis for Proteinuria	UPC ^d
Thyroid Function Test	TSH ^e

- a) Estimated creatinine clearance should be calculated using the Cockcroft and Gault method. Alternatively, creatinine clearance can be measured directly by 24-hour urine collection.
- b) A direct bilirubin level should be obtained if the total bilirubin level is greater than 1.5 X upper limit of normal (ULN). See Section 7 for stopping criteria and dose modification guidelines for treatment-emergent liver function abnormality.
- c) Coagulation tests may also be performed in response to an AE/SAE of bleeding and as clinically indicated.
- d) UPC should be evaluated as described in Appendix A or by 24-hour urine protein. If $UPC \geq 3$ or if urine protein is $\geq 3g$, then the dose modification table guidelines should be followed (7.1).
- e) Unscheduled thyroid function tests [TSH and thyroxine (free T₄)] should be performed if clinically indicated (e.g., if a subject develops signs and symptoms suggestive of hypothyroidism).

10.5 Stopping Rules

A delay in surgery exceeding 7 days as a consequence of pazopanib-related toxicity will be considered an unacceptable toxicity. If the number of unacceptable toxicities exceeds 1 in the first 3 patients, or exceeds 2 in the first 6 patients or more than 25% thereafter, the study will hold accrual for an amendment regarding treatment modifications or study termination. Toxicity will be graded and recorded for each patient in this population according to CTCAE 4.0.

An interim analysis will occur after 16 patients have completed the 30 day post-surgical evaluation period (see section 11.1). The DSMC will review the results of the interim analysis to determine if the study should be allowed to continue or be stopped for excessive post-surgical toxicity due to pazopanib in the treatment arm.

11 STATISTICAL CONSIDERATIONS

In multivariate analysis, VEGFR1+ clustering in pelvic lymph nodes was an independent predictor of time to biochemical recurrence, with an optimal cutoff of 1.65 clusters/hpf [4]. The primary hypothesis for this study is that treatment with pazopanib (as compared to control) will result in a decrease in pre-metastatic niche formation, as characterized by VEGFR1+ cell clusters, in pelvic lymph nodes. The primary efficacy endpoint will be the mean number of VEGFR1+ clusters in pelvic lymph nodes. The mean number of VEGFR1+ clusters per high power field in the study described above was 3.13, with a standard deviation SD = 1.43 and a range of 0 – 6.25. With 15 subjects per arm (30 subjects in all) there will be 80% power to detect a difference of 1.33 in the mean number of VEGFR1+ clusters/hpf between the reference and experimental arms using a student's t-test at the one-sided alpha = 0.05 significance level. Assuming the number of clusters/hpf follows a Gaussian distribution, this difference corresponds a substantial improvement from 15% of subjects with <1.65 clusters/hpf in the standard therapy arm to 46% of subjects with <1.65 clusters/hpf in the experimental therapy arm.

Progression-free survival will be a secondary efficacy endpoint. PFS will be analyzed descriptively using Kaplan-Meier methods and associated 95% confidence intervals.

Exploratory biomarker endpoints will be compared between the arms using student's t-tests (provided the data is normally distributed) or a non-parametric Wilcoxon test (if the data is non-normally distributed). Safety outcomes will be tabulated.

11.1 Interim analysis for post-surgical complications

An interim analysis will be performed after 16 patients have completed the follow-up toxicity assessment at ≥ 30 days post-surgery. If the number of patients with Grade III-V surgical complications by the Clavien-Dindo system differs by two or more between the study arms then the study will be held until full review by the DSMC. The operating characteristics of this stopping rule were assessed via simulation (100,000 simulations per condition). The proportion of patients with grade III or higher Clavien-Dindo complications is less than 15%. If the true proportion of grade III-V Clavien-Dindo complications in both arms is 10% the probability of stopping is 19%. If the true proportion of grade III-V Clavien-Dindo complications are 10% and 40% in the two arms then the probability of stopping is 72%.

For reference to Clavien-Dindo system:

http://www.uroweb.org/fileadmin/livesurgery/Clavien-Dindo_Table.pdf

12 REGISTRATION GUIDELINES

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Patients must not have any study procedures or begin protocol treatment prior to registration.

Treatment should start within five working days after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to: CTORegistrations@hci.utah.edu.

13 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

14 SPECIAL INSTRUCTIONS

14.1 Flow Cytometry Procedure

Flow cytometric quantification of regulatory T cells, cytotoxic T cells and myeloid derived suppressor cells in pelvic lymph nodes from high risk prostate cancer patients

- 13.1.2 Lymph nodes will be minced then dissociated by treatment with collagenase (Invitrogen) according to the manufacturer's protocol to create single cell suspensions. Subsequently, staining will be performed for cytotoxic T cells (CTCLs), regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSC) as follows.
Approximately 1×10^6 lymph node cells in 100 μ L of Staining Buffer (PBS, 0.1% BSA, 0.1% NaN_3) will be placed in each of three tubes. CTCLs will be evaluated by staining for CD45, CD3, CD8, and

granzyme B. First, fluorochrome conjugated anti-human CD45, anti-CD3 and anti-CD8 will be added to the cell suspensions then incubated for 20 min at room temperature in the dark. After incubation, cells will be washed with staining buffer, then fixed and permeabilized using a commercially available fixation and permeabilization kit (eBioscience) according to manufacturer's protocol and additionally stained with anti-Granzyme B by incubating for 40 min at 4°C in the dark. Cells will then be washed with staining buffer then resuspended in 500 µL of staining buffer and analyzed by flow cytometry. A second aliquot of lymph node cells will be stained for CD45, CD3, CD4 and FOXP3 to identify Tregs. First, cells will be incubated with anti-CD45, anti-CD3 and anti-CD4 for 20 min at room temperature in the dark. After incubation, cells will be washed with staining buffer, fixed and permeabilized using the above kit according to manufacturer's protocol and additionally stained with anti-FOXP3 by incubating for 40 min at 4°C in the dark. Subsequently, cells will be washed with staining buffer then resuspended in 500 µL of staining buffer and analyzed by flow cytometry. MDSCs will be identified by staining cells for CD11b, CD33, CD14 and HLA-DR by incubating with fluorochrome conjugated antibodies for 20 min at room temperature in the dark. Cells will be washed with staining buffer, resuspended in 500 µL of staining buffer and analyzed by flow cytometry. All flow cytometry antibodies will be purchased from eBioscience. Tregs have the phenotype CD3+, CD4+, FOXP3+. CTLs have the phenotype, CD3+, CD8+, granzyme B+. Monocytic MDSCs have the phenotype CD11b+, CD33+, HLA-DR low/-, CD14+ and granulocytic MDSCs have the phenotype CD11b+, CD33+, HLA-DR low/-, CD14-. For comparison between patients, all of these subsets will be expressed as percent of total lymph node cells.

Lymph node samples (1-2 fresh, not frozen, benign pelvic lymph nodes) for Flow Cytometry should be sent to the following:

Todd Kelley, PhD:
Attn: Olga Efimova in Hematopathology
University of Utah
Department of Pathology
15 North Medical Drive East
Salt Lake City, UT 84112

14.2 Correlative Studies

Analysis of pre-metastatic niche density will take place through previously reported techniques. Briefly, a total of 15 10 µm sections of benign lymph node tissue (derived from paraffin-embedded sections) will be stained with monoclonal antibodies directed at VEGFR1 (ImClone Systems). VEGFR1 clustering will be counted within 8 distinct 40x fields, and the cluster count will be averaged.

14.3.1 Time Points for collection:

- Tissue will be obtained at the time of prostatectomy/PLND.

14.3.2 Required samples

- Tissue: 15 paraffin-embedded slides derived from normal lymph node tissue will be requested. These slides will be marked with a unique patient identifier number (UPIN) designated by the pathology core facility. Only the study PI and biostatistician will have access to the data to correlate UPIN with patient identification; this data will be housed in a password-protected electronic database.

Tissue will be stored by TRAC and may be batched and sent to the following:

Sumanta Pal, MD
Department of Medical Oncology & Experimental Therapeutics
City of Hope Comprehensive Cancer Center
1500 East Duarte Road
Duarte, CA 91010

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

15.2 Institutional Review

Study will be approved by the Institutional Review Board of University of Utah.

15.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) and approved by the NCI to assure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. Roles and responsibilities of the DSMC are set forth in the NCI approved plan. The activities of this committee include a quarterly review of adverse events including SAEs, important medical events, significant revisions or amendments to the protocol, and approval of cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

All **phase II** studies are reviewed by the full committee at each quarterly DSMC meeting. This includes a review of all serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates as well as all grade 3 or greater toxicities for patients on treatment and within 30 day follow-up window (only if possibly, probably or definitely related).

15.4 Adverse Events / Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for AE and SAE reporting. An electronic copy of the CTCAE Version 4.0 can be downloaded from:

<http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx>

15.4.1 Adverse Events (AE)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Events meeting the definition of an AE include:

1. Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator
2. Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
3. New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
4. Signs, symptoms, or the clinical sequelae of a suspected interaction
5. Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE)

“Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. However, the signs and

symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that do not meet the definition of an AE include:

1. Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
2. The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
3. Medical or surgical procedure (e.g., prostatectomy); the condition that leads to the procedure is an AE
4. Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
5. Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

The collection of adverse events will begin after the first dose of study treatment. Adverse event collection will end 1 month post-prostatectomy.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade based on CTCAE v.4 (grade 1-5)
2. its relationship to the study drug(s) (definite, probable, possible, unlikely, not related)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication

taken; non-drug therapy given; hospitalization/prolonged hospitalization)

5. whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 7 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the pazopanib is described in the Drug Information (section 3) and the most recent Investigator Brochure as well as the FDA-approved product labels. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

15.4.2 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- results in persistent or significant disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- is medically significant: medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers,

intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- causes congenital anomaly or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious

Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.
- All events meeting liver stopping criteria must be recorded as an SAE.
- However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

Disease-Related Events and/or Disease-Related outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

Collection of SAEs

The collection of serious adverse events will begin after the first dose of study treatment. Serious adverse event collection will end 1 month post-prostatectomy.

Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart.

15.5 SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, the IRB, and Novartis, according to the requirements described below:

A MedWatch 3500A form must be completed and submitted to compliance@hci.utah.edu as soon as possible, but no later than 10 days of first knowledge or notification of event (5 days for fatal or life threatening event). Please note that Novartis reporting is required within 24 hours of learning of the event. In place of the Medwatch, the Novartis SAE report form may be used for DSMC reporting purposes. If the SAE meets FDA reporting requirements, then a MedWatch 3500A must also be completed.

*Medwatch 3500A form can be found at <http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/ucm082728.pdf>

DSMC Notifications:

- An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for each individual study.
- The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the quarterly DSMC meeting.

FDA Notifications:

- Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:
 - Serious
 - Unexpected

- Definitely, Probably or Possibly Related to the investigational drug
- Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.
- All other events that meet the criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.
- The RCO will review the MedWatch report for completeness, accuracy and applicability to the regulatory reporting requirements.
- The RCO will ensure the complete, accurate and timely reporting of the event to the FDA.
- The Regulatory Coordinator will submit the report as an amendment to the IND application.
- All other adverse events and safety information not requiring expedited reporting that occur or are collected during the course of the study will be summarized and reported to the FDA through the IND Annual Report.
- IRB Notification: Events meeting the University of Utah IRB reporting requirements (<http://www.research.utah.edu/irb/>) will be submitted through the IRB's electronic reporting system within 10 working days.
- Novartis/Drug Manufacturer Notifications: Once an investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to Novartis within 24 hours of being notified of the event. All SAEs regardless of relationship to investigational product will be collected from the first dose of investigational product to at least 30 days after the last dose of study treatment. All SAEs regardless of causality will be collected until the end of the follow-up period. From the time a subject consents to participate in and completes the study all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to Novartis concomitant medication, will be reported promptly to Novartis. Any SAE brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to investigational product must be reported to Novartis.

SAE's should be reported to Novartis alone with the Novartis SAE Fax cover sheet. All applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to pazopanib treatment and sign the form. The completed SAE form should be sent to the following with the Novartis FAX cover sheet:

Oncology Novartis DS&E department
Fax: 1-877-778-9739

15.6 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

15.7 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

15.8 FDA Annual Reporting

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. (21 CFR 312.33). Content of this report is listed in Appendix III.

15.9 Clinical Trials Data Bank

The study will be registered on <http://clinicaltrials.gov> and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

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Appendix A: UPC

Clinical meaning of UPC

There is a good correlation between the ratio of protein concentration to creatinine concentration in a random urine sample and the amount of protein excreted over 24 hours. Creatinine excretion is fairly constant throughout the day regardless of changes in urine flow rate.

Men excrete 20 mg to 25 mg of creatinine/kg of body weight/day.

Women excrete 15 mg to 20 mg of creatinine/kg of body weight/day.

Normal protein excretion is <100 mg to 150 mg/24 hours and is similar for men and women.

Calculating UPC

UPC ratio = Urine protein (mg/dL) / Urine creatinine (mg/dL).

UPC ratio \approx equivalent to grams of protein excreted in urine over 24 hrs.

Example: Patient has a urine protein = 90 mg/dL and urine creatinine = 30 mg/dL.

UPC ratio = $(90 \text{ mg/dL}) / (30 \text{ mg/dL}) = 3$

The calculated UPC ratio is 3, which correlates to roughly 3 g protein excretion in a 24-hour period.

Units for UPC ratio

Note: To calculate UPC, protein and creatinine concentrations must be expressed in the same units (mg/dL, g/L, or $\mu\text{mol/L}$). If, for example, protein concentration is expressed in mg/dL and creatinine concentration is expressed in $\mu\text{mol/L}$, conversion of one of the concentration values is required. Conversion factors are:

From	To	Conversion Factor
Conventional Units: mg/dL	SI Units: $\mu\text{mol/L}$	Multiply by 88.4
SI Units: $\mu\text{mol/L}$	Conventional Units: mg/dL	Divide 88.4

Appendix B: Drugs with risk to prolong QT interval sorted by generic name

Drugs with known risk	Drugs with possible risk	Drugs with conditional risk
Amiodarone	Alfuzosin	Amantadine
Arsenic trioxide	Artemimol + piperazine	Amisulpride
Azithromycin	Atazanavir	Amitriptyline
Bepiridil	Bedaquiline	Chloral hydrate
Chloroquine	Clozapine	Ciprofloxacin
Chlorpromazine	Dolasetron	Clomipramine
Cisapride	Dronedarone	Desipramine
Citalopram	Eribulin	Diphenhydramine
Clarithromycin	Famotidine	Doxepin
Disopyramide	Felbamate	Fluconazole
Dofetilide	Fingolimod	Fluoxetine
Domperidone	Foscarnet	Glantamine
Droperidol	Fosphenytoin	Imipramine
Erythromycin	Gatifloxacin	Intraconazole
Escitalopram	Gemifloxacin	Ketoconazole
Flecainide	Granisetron	Nortriptyline
Halofantrine	Iloperidone	Paroxetine
Haloperidol	Indapamide	Protriptyline
Ibutilide	Isradipine	Quinine Sulfate
Levomethadyl	Lapatinib	Ritonavir
Mesoridazine	Levofloxacin	Sertraline
Methadone	Lithium	Solifenacin
Moxifloxacin	Mirtazapine	Trazodone
Pentamidine	Moexipril/HCTZ	Trimethoprim-Sulfa
Pimozide	Nicardipine	Trimipramine
Probucol	Nilotinib	
Procainamide	Ofloxacin	
Quinidine	Olanzapine	
Sevoflurane	Ondansetron	
Sotalol	Oxytocin	
Sparfloxacin	Paliperidone	
Terfenadine	Perflutren lipid microspheres	
Thioridazine	Promethazine	
	Quetiapine	
	Ranolazine	
	Risperidone	
	Roxithromycin	
	Saquinavir	
	Sertindole	
	Sunitinib	
	Tacrolimus	
	Tamoxifen	
	Telithromycin	
	Tizanidine	
	Tolterodine	
	Vardenafil	
	Venlafaxine	
	Voriconazole	
	Ziprasidone	

APPENDIX C: NEW YORK HEART ASSOCIATION (NYHA) GUIDELINES

NYHA Classification

Excerpted from Oxford Textbook of Medicine. Vol 2, p.2228. Oxford Press.1997.

Class	Description
I	Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Subjects with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.